

***Remarks***

Claims 142-149, 151-154, and 161 are canceled herein, the subject matter of claim 161 having been incorporated into claim 141. Applicants reserve the right to claim the subject matter of canceled claims 142-149 and 151-154 in continuing applications. Claims 141 and 162-164 are amended herein and new claims 165-173 are added herein.

Support for the amendments can be found, *inter alia*, at page 5, line 10, and Table 1 of the specification. Support for the new claims can be found, *inter alia*, at page 4, lines 31-32, page 5, line 25 through page 6, line 9, and page 14, lines 5-10. No new matter has been added by way of these amendments or new claims. Claims 141, 150, 155-160 and 162-173 are pending in the application.

**I. *Specification***

The Examiner has noted that Generic terminology does not accompany the trademark term “SYBR.” (Office Action, page 2.) Applicants thank the Examiner for pointing out this oversight and have amended the specification to include the generic terminology for “SYBR Green.”

**II. *Rejection of the claims under 35 U.S.C. § 112***

Claim 158 stands rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter. (Office Action, page 2.) Specifically, the Examiner notes that claim 158 recites a trademark. Claim 158 has been amended herein to recite the generic terminology for the trademark.

Claims 141 and 150-164 stand rejected under 35 U.S.C. § 112, first paragraph for failing to comply with the written description requirement. (Office Action, page 3.) Applicants respectfully disagree but in order to facilitate prosecution have amended the claims.

The Examiner asserts that the nucleic acid ladder of claim 141 and 150-164 can have virtually any upper limit as well as any lower limit. (Office Action, page 3.) Claim 141 has been amended to recite “each fragment having a size in base pairs of between 20 kb and 100 base pairs.”

In view of the above Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 112.

**III. Rejection of claims under 35 U.S.C. §§ 102 and 103**

Claims 141-157 and 159-164 stand rejected under 35 U.S.C. § 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. § 103(a) as obvious over Carlson *et al.* (U.S. Patent No. 5,316,908) or Strategene (1993) or Strategene Catalog (1993). (Office Action, page 4.) Applicants respectfully disagree but in order to facilitate prosecution have amended the claims and added new claims.

For the purposes of examination, the Examiner has construed the claims to encompass not only those fragments that have substantially equivalent relative mass but those that do not have substantially equivalent relative mass based on the inclusion of the term “comprising” in claim 141. (Office Action, page 4.) In order to more clearly focus the claim, Applicants have replaced the term “comprising” with the term “consisting of” in claim 141.

The Examiner has further construed the term “substantially equivalent” as allowing for a 6 fold range in relative mass and/or signal intensity. (Office Action, page 5.) This is based on the reasoning that there may be “a 3 fold increase and/or decrease over a set value.” The Examiner’s construction is in conflict with the specification. At page 9, lines 8-10, the specification states “[r]elative mass is substantially equal when the relative mass of each fragment is no more than 3 times the relative mass of another fragment.” There is no reference to a “set value” in relation to a range, therefore the range is 3 fold not 6 fold as the Examiner asserts.

The Examiner asserts that Figure 1 of Carlson *et al.* discloses a nucleic acid ladder that meets the limitations of claims 141-157 and 159-164. (Office Action, page 5.) In particular, the Examiner asserts that “[s]aid Figure clearly shows that the bands have the same relative density.”

Carlson *et al.* fails to disclose bands having the same relative mass. Carlson *et al.* discloses nucleic acid ladders having even spacing between bands and in which the bands are detected using a labeled probe. (see Summary of the Invention in Carlson *et al.*.) The DNA fragments (target DNA) are designed such that each band contains the same “S” sequence to which the labeled probe hybridizes. As noted at column 3, lines 34-35 of Carlson *et al.*, “[p]referably, the target DNA is constructed from a single bacteriophage or plasmid.” One skilled in the art would recognize that DNA fragments derived from the same bacteriophage or

plasmid would not have substantially equivalent mass. Further, as described at column 4, lines 35-41, when the total DNA of the Carlson *et al.* ladder kits is stained with ethidium bromide (as the DNA in the instant application may be stained) a smear is obtained, not discrete bands. Therefore, the bands of Carlson *et al.* do not have the same relative density because each band has the same relative mass but because each band has the same "S" sequence to which the labeled probe hybridizes.

Carlson *et al.* also alters the copy number of the largest and the smallest fragments in the ladder by increasing their copy number relative to the copy number of the middle range fragments (column 5, lines 55-63 of Carlson *et al.*). This alteration is described by Carlson *et al.* as one that overcomes the poor hybridization efficiency of the larger fragments and the poor retention of the smaller fragments on a membrane. If one were to increase the copy number of the larger fragments relative to the medium sized fragments (as described by Carlson *et al.*), both the relative mass and the total mass of the larger fragments would be increased in comparison to other fragments in the ladder. Because the claims prosecuted herein require that the relative mass of each fragment in the ladder be substantially equal, Carlson *et al.* fails to disclose all of the limitations of these claims.

In addition, as discussed above, the increase in copy number of the larger fragments compared to the medium-sized fragments would lead to an increase in the relative mass or the total mass of the larger fragments, rather than a mass that is substantially equal as claimed herein. Applicants have demonstrated in Figure 2 of the instant application that several commercially available nucleic acid ladders meet this size requirement. However, neither this figure or the other ladders disclosed in Figure 2, describe the relative mass requirements recited in the instant claims. Figure 1 of Carlson *et al.* is a drawing which merely lists a range of nucleic acid fragments, irrespective of the relative mass of each of those fragments. Furthermore, as evidenced by the multitude of commercially-available DNA ladders disclosed in Figure 2 of the specification that fail to meet this requirement, the need had not been met in the art. Thus, the Examiner has failed to provide a *prima facie* case of obviousness.

New independent claim 165 is directed, in part, to a nucleic acid ladder comprising fragments with specific sizes in base pairs and having a copy number such that each fragment has a relative mass that is substantially equal. New independent claim 169 further recites a highlight fragment having a relative mass that is three times greater than the other fragments.

Carlson *et al.* does not disclose the specific fragments recited in claims 165 and 169 and, as discussed above, does not disclose fragments having substantially equal relative mass. In addition Carlson *et al.* does not disclose a ladder with a highlight fragment as recited in claim 169. Therefore, Applicants believe that new claims 165-173 are not anticipated or rendered obvious by the cited art.

In view of the above, Applicants respectfully request reconsideration and withdrawal of the rejection of the claims under 35 U.S.C. § 102(b) or 35 U.S.C. § 103(a). If the Examiner still has concerns regarding the claims, Applicants respectfully request that the Examiner contact the undersigned for an interview.

***Conclusion***

Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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